PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Long-term early development research in congenital heart disease (LEADER-CHD): A study protocol for a prospective cohort observational study investigating the development of children after surgical correction for congenital heart defects during the first three years of life
AUTHORS	Ferentzi, Hannah; Pfitzer, Constanze; Rosenthal, Lisa-Maria; Berger, Felix; Schmitt, Katharina

VERSION 1 – REVIEW

REVIEWER	Mohammad El Tahlawi Assisstant Professor of Cardiology Zagazig University Zagazig-Egypt Fellow of Academy of Scientific Research & Technology Cairo-Egypt Tel: 0020/1005268764
REVIEW RETURNED	03-Sep-2017

GENERAL COMMENTS	The authors of the current protocool aim to investigate long-term early development of children with different congenital heart defects during the first three years of life. They chose the biventricular pathology in 3 different forms to conduct their study. First I thank the authors for this interesting well written protocool. -Minor concern: The authors' objectives are to measure cognitive, language and motoric development, therefore they used 2 cyanotic models and one acyanotic pathology (VSD). This VSD pathology, even if it is corrected ealy in life , it should be clearly notified that it was still in corrective stage before any Eisenmenger pathophysiology to be developped. -Major concern: As long as the study searches for the factors affecting the motoric and cognitive development in CHD children, I think that it is better to choose one group that would be expected to have developmental affection due to decrease systemic blood supply; as in case of aortic coarctation, congenital aortic stenosis, subaortic membrane with subaortic stenosis, HLHS...etc. This category will be more representative to CHD that affect the development. Therefore, if the study is not ongoing yet, I suggest to add one of these diseases in the other arm of CHD besides biventricular pathology. This biventricular pathology could be reclassified into cyanotic and acuanotic CHD.

REVIEWER	Andrea Szekely MD PhD Semmelweis University Budapest Department of Anesthesiology and Intensive Care, Hungary
REVIEW RETURNED	11-Oct-2017

GENERAL COMMENTS	The study proposal is well written and concise. The power calculation is good. I am not sure that the Bailey test will be enough to differentiate, but there are really no exact data about it. I have two suggestions. First, try to enroll patients with PDA closure and alternatively patients, who do not require cardiopulmonary bypass (also each 40-40 patients). You could have on this way at least two quasi control groups (i.e. a corrective surgery and a group without CPB). Why have you excluded univentricular heart physiology from the data collection? Second, I would collect info about the type, dose and length of anesthetics, analgesics and sedatives. Similarly collect data about hypoxic events and hypotension in the postoperative period. Just think about the neurotoxicity. Similarly last CO2 level, saturation at discharge would be important. I wish good luck and endurance for the study

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer: 1

Dear Dr El Tahlawi,

Thank you very much for taking the time to read the manuscript and for your valuable comments.

>>> Re minor concern: We only include patients who undergo corrective surgery during infancy, before the age of 10 months (see inclusion and exclusion criteria in the manuscript). Consequently, the heart defect is corrected before it causes significant pulmonary hypertension in our sample. As this might not have been stated clearly enough in our manuscript, we have made it more explicit, as you suggested (see page 5 and 7).

>>> Re major concern: Data collection is already ongoing, so unfortunately we cannot include the suggested patient groups in our study. However, we agree that it would be very interesting to look at other heart defects, especially HLHS. Therefore, we are currently preparing to investigate early development also in this patient group, using the same study design.
We decided against reclassifying biventricular physiology into acyanotic and cyanotic CHD for our main analysis, because we are interested in potential differences between patients with tetralogy of Fallot and patients with transposition of the great arteries. Generally, patients with CHD are at risk for brain injury and developmental disorders. This risk is multifactorial and probably synergistic (see, for instance a review by Marelli and colleagues, 2016). Proposed mechanisms of impaired neurodevelopment are reduced cerebral oxygenation and perfusion, while the relative contributions probably differ among forms of CHD (see, for instance, Rollins, 2016). Accordingly, differences in developmental dynamics might be expected even within the group of cyanotic heart defects, depending on the specific heart defect. Only few studies have focused on this issue, so we hope to add insight into the developmental sequelae of specific cyanotic heart defects.

Again, thank you very much for your valuable comments! We hope to have clarified the issues you mentioned to your satisfaction and we are looking forward to sharing our results.

Response to Reviewer: 2

Dear Dr Szekely,

Thank you very much for taking the time to read the manuscript and for your valuable comments.

>>> Re first suggestion: We agree that a control group of patients without open heart surgery would provide a useful option for comparison. As data collection is already ongoing, we cannot include the suggested patient groups in our study. However, when we developed the study design, we decided against recruiting a control group for two reasons. Firstly, the Bayley III test is standardized based on a large normative sample, therefore providing useful reference for our first aim (which is to investigate whether there are clinically relevant developmental delays at ages 12, 24 and 36 months). Secondly, we chose to focus on developmental aspects in this study, with a threefold second aim: (a) investigating differences in Bayley III scores across time between our three surgical groups (by using repeated measures analysis, as specified in our manuscript); (b) investigating predictors of cognitive, motoric and language scores at certain ages (by using multiple regression analyses); (c) investigating predictors of development across time (by using multilevel modelling as secondary analysis). All these research questions can be answered without relying on a control group.
Your question about univentricular heart physiology was also a concern of the first reviewer. As data collection is already ongoing, we cannot include the suggested patient groups in our study, but we are currently preparing to investigate early development in an HLHS patient group, using a similar study design.

>>> Re second suggestion: Medical data on type, dose and duration of anesthetics, analgesics and sedatives, as well as CO2 levels and oxygen saturation at discharge are available for all our patients, so we are glad to follow your suggestion to add them to our protocol (see page 9 of our manuscript). In our study, we register neurological events as one of the indicators of the post-operative course. This variable includes hypoxic events (i.e., cerebral infarction, global cerebral ischemia). For clarification, we have added this to our manuscript. We also register resuscitations (i.e., as consequence of respiratory failure/ hypoxia or hypoperfusion/ cardiogenic shock). By measuring these variables, we hope to have included all clinically relevant entities.

Again, thank you very much for your valuable comments! We hope to have solved all issues to your satisfaction and we are looking forward to sharing our results.

VERSION 2 – REVIEW

REVIEWER	Mohammad El Tahlawi Zagazig University, Egypt
REVIEW RETURNED	05-Dec-2017

GENERAL COMMENTS	Thank you for your reply. I think it seems satisfactory.